

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION					
<small>DISTRICT ADDRESS AND PHONE NUMBER</small> 250 Marquette Ave, Ste. 600 Minneapolis, MN 55401 (612) 334-4100 Fax: (612) 334-4134		<small>DATE(S) OF INSPECTION</small> 4/9/2019-4/23/2019* <small>FEI NUMBER</small> 3015213291			
<small>NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED</small> <div style="background-color: black; width: 150px; height: 1.2em; display: inline-block;"></div> Sponsor-Investigator					
<small>FIRM NAME</small> <div style="background-color: black; width: 150px; height: 1.2em; display: inline-block;"></div> Sponsor-Investigator		<small>STREET ADDRESS</small> Hennepin County Medical Center, Dept Of Emergency Medicine, 701 Park Ave			
<small>CITY, STATE, ZIP CODE, COUNTRY</small> Minneapolis, MN 55415-1623		<small>TYPE ESTABLISHMENT INSPECTED</small> sponsor-investigator			
<p>This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.</p>					
<p><b>DURING AN INSPECTION OF YOUR FIRM I OBSERVED:</b>  <b>OBSERVATION 1</b>            The sponsor failed to submit an IND to the FDA prior to conducting a clinical investigation with an investigational new drug.</p> <p>Specifically, study <div style="background-color: black; width: 150px; height: 1.2em; display: inline-block;"></div> and <div style="background-color: black; width: 100px; height: 1.2em; display: inline-block;"></div> were conducted without submitting INDs.</p>					
<p><b>OBSERVATION 2</b>            Legally effective informed consent was not obtained from a subject or the subject's legally authorized representative, and the situation did not meet the criteria in 21 CFR 50.23 - 50.24 for exception.</p> <p>Specifically, subjects were enrolled and treated on the following studies without obtaining informed consent, with neither study appearing to meet the criteria for exception from informed consent:</p> <p>A. <div style="background-color: black; width: 150px; height: 1.2em; display: inline-block;"></div> - 747 subjects; and,</p> <p>B. <div style="background-color: black; width: 150px; height: 1.2em; display: inline-block;"></div> - at least 874 subjects.</p>					
<p><b>OBSERVATION 3</b>            Not all changes in research activity were approved by an Institutional Review Board prior to implementation.</p> <p>Specifically,</p>					
<b>SEE REVERSE OF THIS PAGE</b>		<table border="0" style="width: 100%;"> <tr> <td style="width: 60%; vertical-align: top;"> <small>EMPLOYEE(S) SIGNATURE</small>            Sharon L Matson, Investigator         </td> <td style="width: 40%; vertical-align: top;"> <div style="text-align: center;"> <small>Sharon L. Matson Investigator Signed By: Sharon L. Matson -S Date Signed: 04-23-2019 13:11:59</small>            X         </div> </td> </tr> </table>		<small>EMPLOYEE(S) SIGNATURE</small> Sharon L Matson, Investigator	<div style="text-align: center;"> <small>Sharon L. Matson Investigator Signed By: Sharon L. Matson -S Date Signed: 04-23-2019 13:11:59</small>            X         </div>
<small>EMPLOYEE(S) SIGNATURE</small> Sharon L Matson, Investigator	<div style="text-align: center;"> <small>Sharon L. Matson Investigator Signed By: Sharon L. Matson -S Date Signed: 04-23-2019 13:11:59</small>            X         </div>				
<small>DATE ISSUED</small> 4/23/2019					

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION																							
<small>DISTRICT ADDRESS AND PHONE NUMBER</small> 250 Marquette Ave, Ste. 600 Minneapolis, MN 55401 (612) 334-4100 Fax: (612) 334-4134		<small>DATE(S) OF INSPECTION</small> 4/9/2019-4/23/2019* <small>FBI NUMBER</small> 3015213291																					
<small>NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED</small> <div style="background-color: black; width: 150px; height: 1.2em; display: inline-block;"></div> Sponsor-Investigator																							
<small>FIRM NAME</small> <div style="background-color: black; width: 150px; height: 1.2em; display: inline-block;"></div> Sponsor-Investigator		<small>STREET ADDRESS</small> Hennepin County Medical Center, Dept Of Emergency Medicine, 701 Park Ave																					
<small>CITY, STATE, ZIP CODE, COUNTRY</small> Minneapolis, MN 55415-1623		<small>TYPE ESTABLISHMENT INSPECTED</small> sponsor-investigator																					
<p>A. For study <div style="background-color: black; width: 150px; height: 1.2em; display: inline-block;"></div></p> <p>1. Serious adverse events (SAEs) were not reported to the IRB as required by the IRB, e.g.:</p> <table style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left; width: 15%;"><u>Subject#</u></th> <th style="text-align: left;"><u>SAE</u></th> </tr> </thead> <tbody> <tr><td>6</td><td>airway complication, required intubation</td></tr> <tr><td>26</td><td>hypoxia, required nasal cannula oxygen</td></tr> <tr><td>37</td><td>hypoxia, required nasal cannula oxygen, nasal/oral airway, and jaw thrust</td></tr> <tr><td>300</td><td>hypoxia, required nasal cannula oxygen, face mask oxygen, and nasal/oral airway</td></tr> <tr><td>346</td><td>hypoxia, required nasal cannula oxygen</td></tr> <tr><td>498</td><td>airway complication, required intubation</td></tr> <tr><td>594</td><td>pupils became pinpoint</td></tr> <tr><td>619</td><td>hypoxia, required intubation</td></tr> <tr><td>621</td><td>dystonia.</td></tr> </tbody> </table> <p>2. An additional treatment regimen was added to the study, using treatment Haloperidol at 10 mg from 9/21/2017 to 10/12/2017, without IRB review or approval.</p>				<u>Subject#</u>	<u>SAE</u>	6	airway complication, required intubation	26	hypoxia, required nasal cannula oxygen	37	hypoxia, required nasal cannula oxygen, nasal/oral airway, and jaw thrust	300	hypoxia, required nasal cannula oxygen, face mask oxygen, and nasal/oral airway	346	hypoxia, required nasal cannula oxygen	498	airway complication, required intubation	594	pupils became pinpoint	619	hypoxia, required intubation	621	dystonia.
<u>Subject#</u>	<u>SAE</u>																						
6	airway complication, required intubation																						
26	hypoxia, required nasal cannula oxygen																						
37	hypoxia, required nasal cannula oxygen, nasal/oral airway, and jaw thrust																						
300	hypoxia, required nasal cannula oxygen, face mask oxygen, and nasal/oral airway																						
346	hypoxia, required nasal cannula oxygen																						
498	airway complication, required intubation																						
594	pupils became pinpoint																						
619	hypoxia, required intubation																						
621	dystonia.																						
<b>SEE REVERSE OF THIS PAGE</b>		<small>EMPLOYEE(S) SIGNATURE</small> Sharon L Matson, Investigator  <div style="text-align: right;"> <small>Sharon L Matson Investigator Signed by Sharon L Matson -S Date Signed: 04-23-2019 13:11:59</small>            X         </div>																					
<small>FORM FDA 483 (09/08)</small>		<small>PREVIOUS EDITION OBSOLETE</small>																					
<small>INSPECTIONAL OBSERVATIONS</small>		<small>PAGE 2 of 7 PAGES</small>																					

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION																					
<small>DISTRICT ADDRESS AND PHONE NUMBER</small> 250 Marquette Ave, Ste. 600 Minneapolis, MN 55401 (612) 334-4100 Fax: (612) 334-4134		<small>DATE(S) OF INSPECTION</small> 4/9/2019-4/23/2019* <hr/> <small>FEI NUMBER</small> 3015213291																			
<small>NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED</small> <div style="background-color: black; width: 200px; height: 1.2em; display: inline-block;"></div> Sponsor-Investigator																					
<small>FIRM NAME</small> <div style="background-color: black; width: 200px; height: 1.2em; display: inline-block;"></div> Sponsor-Investigator		<small>STREET ADDRESS</small> Hennepin County Medical Center, Dept Of Emergency Medicine, 701 Park Ave																			
<small>CITY, STATE, ZIP CODE, COUNTRY</small> Minneapolis, MN 55415-1623		<small>TYPE ESTABLISHMENT INSPECTED</small> sponsor-investigator																			
<p>3. Seven-hundred and forty-seven (747) subjects in total were enrolled and treated on study a) over the 500 approved by the IRB, and b) over the 737 reported as the total enrollment to the IRB.</p> <p>4. An IRB-required annual progress report was not submitted until about 6/29/2018, past the 5/22/2018 expiration of approval.</p> <p>B. For study <div style="background-color: black; width: 150px; height: 1.2em; display: inline-block;"></div></p> <p>1. Serious adverse events (SAEs) were not reported to the IRB as required by the IRB, e.g.:</p> <table style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left; width: 15%;"><u>Subject#</u></th> <th style="text-align: left;"><u>SAE</u></th> </tr> </thead> <tbody> <tr><td>35</td><td>akathisia</td></tr> <tr><td>56</td><td>hypoxia, required nasal cannula oxygen</td></tr> <tr><td>74</td><td>airway complication, required intubation</td></tr> <tr><td>105</td><td>hypoxia</td></tr> <tr><td>134</td><td>hypoxia</td></tr> <tr><td>157</td><td>hypoxia</td></tr> <tr><td>192</td><td>hypotension</td></tr> <tr><td>197</td><td>hypoxia, required intubation.</td></tr> </tbody> </table> <p>2. A study change was submitted to the IRB and approved to voluntarily suspend study activities effective 7/16/2018, with a subsequent change submitted 11/5/2018 stating the study was closed. However, it appears the study continued with the same treatment regimen and data collection activities</p>				<u>Subject#</u>	<u>SAE</u>	35	akathisia	56	hypoxia, required nasal cannula oxygen	74	airway complication, required intubation	105	hypoxia	134	hypoxia	157	hypoxia	192	hypotension	197	hypoxia, required intubation.
<u>Subject#</u>	<u>SAE</u>																				
35	akathisia																				
56	hypoxia, required nasal cannula oxygen																				
74	airway complication, required intubation																				
105	hypoxia																				
134	hypoxia																				
157	hypoxia																				
192	hypotension																				
197	hypoxia, required intubation.																				
<b>SEE REVERSE OF THIS PAGE</b>		<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 60%; vertical-align: top;"> <small>EMPLOYEE(S) SIGNATURE</small>            Sharon L. Matson, Investigator         </td> <td style="width: 40%; vertical-align: top;"> <small>DATE ISSUED</small>            4/23/2019  <div style="text-align: center; font-size: 0.8em;">             Sharon L. Matson              Investigator              Signed By: Sharon L. Matson -S              Date Signed: 04/23/2019 13:11:39              X           </div> </td> </tr> </table>		<small>EMPLOYEE(S) SIGNATURE</small> Sharon L. Matson, Investigator	<small>DATE ISSUED</small> 4/23/2019 <div style="text-align: center; font-size: 0.8em;">             Sharon L. Matson              Investigator              Signed By: Sharon L. Matson -S              Date Signed: 04/23/2019 13:11:39              X           </div>																
<small>EMPLOYEE(S) SIGNATURE</small> Sharon L. Matson, Investigator	<small>DATE ISSUED</small> 4/23/2019 <div style="text-align: center; font-size: 0.8em;">             Sharon L. Matson              Investigator              Signed By: Sharon L. Matson -S              Date Signed: 04/23/2019 13:11:39              X           </div>																				

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER 250 Marquette Ave, Ste. 600 Minneapolis, MN 55401 (612) 334-4100 Fax: (612) 334-4134	DATE(S) OF INSPECTION 4/9/2019-4/23/2019* FEI NUMBER 3015213291
---	--

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED [REDACTED] Sponsor-Investigator
---

FIRM NAME [REDACTED] Sponsor-Investigator	STREET ADDRESS Hennepin County Medical Center, Dept Of Emergency Medicine, 701 Park Ave
CITY, STATE, ZIP CODE, COUNTRY Minneapolis, MN 55415-1623	TYPE ESTABLISHMENT INSPECTED sponsor-investigator

until at least the most recent enrollment of Subject 874 on 11/19/2018; and, the status of the study is posted on clinicaltrials.gov as "Recruiting". Changes in the study that do not appear to have been approved by the IRB include:

- a) Continuing the study after the 7/16/2018 voluntary suspension submitted and approved;
- b) Discontinuing provision of a Notification of Enrollment to subjects on about 7/16/2018; and,
- c) Enrolling at least 874 subjects in total, over the 800 originally approved by the IRB.

3. An additional AMSS Data Validation sub-study was conducted without IRB review or approval.

**OBSERVATION 4**

An investigation was not conducted in accordance with the investigational plan.

Specifically, not all study conduct was in accordance with the study plans submitted to and approved by the IRB for [REDACTED] and [REDACTED], e.g.:

A. There is no documentation to show all subjects were provided a Notification of Enrollment form, e.g.:

- 1. [REDACTED] subject 1, 7, 9, 14, 15, 23, 46, 48, 161, 179, 197, 205, 299, 326, 332, 464, 511, 587, 593, 594, 607, 613, 631, and 633; and,
- 2. [REDACTED] subject 8, 9, 10, 66, 72, 136, 171, 172, 197, 205, 206, 208, 209, 213, 214, 215, 216, 217, and 874.

B. There is no documentation to show all Research Volunteers (RVs) that conducted study operations were trained, e.g.:

- 1. [REDACTED]  
RV                      conducted study operations with  
ND                      5, 8, 14, 173, 339, 343, 344

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Sharon L Matson, Investigator	DATE ISSUED 4/23/2019
	<div style="text-align: right;"> <small>Sharon L Matson Investigator Signed By: Sharon L. Matson-S Date Signed: 04-23-2019 13:11:59</small>  X </div>	

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION			
<small>DISTRICT ADDRESS AND PHONE NUMBER</small> 250 Marquette Ave, Ste. 600 Minneapolis, MN 55401 (612) 334-4100 Fax: (612) 334-4134		<small>DATE(S) OF INSPECTION</small> 4/9/2019-4/23/2019* <small>FEI NUMBER</small> 3015213291	
<small>NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED</small> <div style="background-color: black; width: 150px; height: 1.2em; display: inline-block;"></div> Sponsor-Investigator			
<small>FIRM NAME</small> <div style="background-color: black; width: 150px; height: 1.2em; display: inline-block;"></div> Sponsor-Investigator		<small>STREET ADDRESS</small> Hennepin County Medical Center, Dept Of Emergency Medicine, 701 Park Ave	
<small>CITY, STATE, ZIP CODE, COUNTRY</small> Minneapolis, MN 55415-1623		<small>TYPE ESTABLISHMENT INSPECTED</small> sponsor-investigator	
MJ                      304, 463, 502  ML                      184, 189, 325, 490  HT                      47; and,  2. <div style="background-color: black; width: 100px; height: 1.2em; display: inline-block;"></div>  <u>RV</u> <u>conducted study operations with</u>  PD                      175  HL                      35  AK                      40, 72  LD                      178, 179, 184  EY                      187, 190, 197.			
<b>OBSERVATION 5</b> Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation and informed consent.  Specifically, for study <div style="background-color: black; width: 150px; height: 1.2em; display: inline-block;"></div> and <div style="background-color: black; width: 100px; height: 1.2em; display: inline-block;"></div> there is no identification in source records to show who conducted: A. screening, and completion of Screening Sheets for either study; B. data collection from EMR, and completion of Chart Review form for either study; and, C. data validation, and completion of the AMSS Data Validation form for study <div style="background-color: black; width: 100px; height: 1.2em; display: inline-block;"></div>			
<b>OBSERVATION 6</b>			
<b>SEE REVERSE OF THIS PAGE</b>	<small>EMPLOYEE(S) SIGNATURE</small> Sharon L Matson, Investigator		<small>DATE ISSUED</small> 4/23/2019  <div style="font-size: 0.8em;">             Sharon L Matson              Investigator              Signed By: Sharon L Matson -S              Date Signed: 04-23-2019 13:15:59              X           </div>



DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION			
DISTRICT ADDRESS AND PHONE NUMBER 250 Marquette Ave, Ste. 600 Minneapolis, MN 55401 (612) 334-4100 Fax: (612) 334-4134		DATE(S) OF INSPECTION 4/9/2019-4/23/2019* FEI NUMBER 3015213291	
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED [REDACTED] Sponsor-Investigator			
FIRM NAME [REDACTED] Sponsor-Investigator		STREET ADDRESS Hennepin County Medical Center, Dept Of Emergency Medicine, 701 Park Ave	
CITY, STATE, ZIP CODE, COUNTRY Minneapolis, MN 55415-1623		TYPE ESTABLISHMENT INSPECTED sponsor-investigator	
<p>Failure to ensure proper monitoring of the study.</p> <p>Specifically, there is no documentation to show any monitoring of study [REDACTED] or [REDACTED]</p>			
<p><b>OBSERVATION 7</b></p> <p>Investigational drug disposition records are not adequate with respect to dates, quantity and use by subjects.</p> <p>Specifically, no clinical investigator-required investigational drug disposition records were maintained for either study [REDACTED] or [REDACTED]</p>			
<p><b>OBSERVATION 8</b></p> <p>Lack of records covering receipt and disposition of an investigational drug.</p>			
SEE REVERSE OF THIS PAGE		EMPLOYEE(S) SIGNATURE Sharon L Matson, Investigator  <div style="text-align: right;"> <small>Sharon L. Matson Investigator Signed By: Sharon L. Matson-S Date Signed: 04-23-2019 13:11:09</small>  X </div>	
FORM FDA 483 (09/08)		PREVIOUS EDITION OBSOLETE	
		INSPECTIONAL OBSERVATIONS	
		PAGE 6 of 7 PAGES	

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION			
DISTRICT ADDRESS AND PHONE NUMBER 250 Marquette Ave, Ste. 600 Minneapolis, MN 55401 (612) 334-4100 Fax: (612) 334-4134		DATE(S) OF INSPECTION 4/9/2019-4/23/2019*	
		FEI NUMBER 3015213291	
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED [REDACTED] Sponsor-Investigator			
FIRM NAME [REDACTED] Sponsor-Investigator		STREET ADDRESS Hennepin County Medical Center, Dept Of Emergency Medicine, 701 Park Ave	
CITY, STATE, ZIP CODE, COUNTRY Minneapolis, MN 55415-1623		TYPE ESTABLISHMENT INSPECTED sponsor-investigator	
Specifically, no sponsor-required investigational drug records were maintained for either study [REDACTED] or [REDACTED]			
<b>*DATES OF INSPECTION</b> 4/09/2019(Tue), 4/10/2019(Wed), 4/11/2019(Thu), 4/15/2019(Mon), 4/16/2019(Tue), 4/17/2019(Wed), 4/18/2019(Thu), 4/23/2019(Tue)			
SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Sharon L Matson, Investigator		DATE ISSUED 4/23/2019
	Sharon L Matson Investigator Signed By: Sharon L Matson -S Date Signed: 04-23-2019 12:11:59 X		

The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."